Genome-wide Study Identifies Association between HLA-B*55 : 01 and Self-Reported Penicillin Allergy

23 Me Res Team

2020-10-01

23 Me Res Team , Krebs , K , Bovijn , J , Zheng , N & Fadista , J 2020 , ' Genome-wide Study Identifies Association between HLA-B*55 : 01 and Self-Reported Penicillin Allergy ' , American Journal of Human Genetics , vol. 107 , no. 4 , pp. 612-621 . https://doi.org/10.1016/j.ajhg.2020.08.008

http://hdl.handle.net/10138/321031
https://doi.org/10.1016/j.ajhg.2020.08.008

Genome-wide Study IdentiÞes Association between HLA-B*55:01 and Self-Reported Penicillin Allergy

Kristi Krebs,[1,2,25] Jonas Bovijn,[3,4,25] Neil Zheng,[5,25] Maarja Lepamets,[1,2] Jenny C. Censin,[3,4] Tuuli Jürgenson,[1] Dage Sæg,[6] Erik Abner,[1] Triin Laisk,[1] Yang Luo,[7,8,9,10,11] Line Skotte,[12] Frank Geller,[12] Bjarke Feenstra,[12] Wei Wang,[13] Adam Auton,[13] 23andMe Research Team,[13] Soumya Raychaudhuri,[7,8,9,10,11,14] Tõnu Esko,[1] Andres Metspalu,[1] Sven Laur,[6,15] Dan M. Roden,[5,16,21] Wei-Qi Wei,[5] Michael V. Holmes,[4,17,18,19,25] Cecilia M. Lindgren,[3,4,17,20,25] Elizabeth J. Phillips,[16,21,22,25] Reedik Mägi,[1,25] Lili Milani,[1,25,*] and João Fadista[12,23,24,25]

Summary

Hypersensitivity reactions to drugs are often unpredictable and can be life threatening, underscoring a need for understanding their underlying mechanisms and risk factors. The extent to which germline genetic variation in uences the risk of commonly reported drug allergies such as penicillin allergy remains largely unknown. We extracted data from the electronic health records of more than 600,000 participants from the UK, Estonian, and Vanderbilt University Medical Center's BioVU biobanks to study the role of genetic variation in the occurrence of self-reported penicillin hypersensitivity reactions. We used imputed SNP to HLA typing data from these cohorts to further ne map the human leukocyte antigen (HLA) association and replicated our results in 23andMe's research cohort involving a total of 1.12 million individuals. Genome-wide meta-analysis of penicillin allergy revealed two loci, including one located in the HLA region on chromosome 6. This signal was further ne-mapped to the HLA-B*55:01 allele (OR 1.41 95% CI 1.33–1.49, p value 2.04 3 10 ^{31}) and con rmed by independent replication in 23andMe's research cohort (OR 1.30 95% CI 1.25–1.34, p value 1.00 3 10 ^{47}). The lead SNP was also associated with lower lymphocyte counts and in silico follow-up suggests a potential effect on T-lymphocytes at HLA-B*55:01. We also observed a signi cant hit in PTPN22 and the GWAS results correlated with the genetics of rheumatoid arthritis and psoriasis. We present robust evidence for the role of an allele of the major histocompatibility complex (MHC) I gene HLA-B in the occurrence of penicillin allergy.

Introduction

Adverse drug reactions (ADRs) are common in clinical practice and are associated with high morbidity and mortality. A meta-analysis of prospective studies in the US revealed the incidence of serious ADRs to be 6.7% among hospitalized patients and the cause of more than 100,000 deaths annually.[1] In Europe, ADRs are responsible for 3.5% of all hospital admissions, with 10.1% of patients experiencing ADRs during hospitalization and 197,000 fatal cases per year.[2,3] In the US, the cost of a single ADR event falls between 1,439 to 13,462 USD.[4]

ADRs are typically divided into two types of reactions. Type A reactions are more predictable and related to the pharmacological action of a drug, whereas type B reactions are idiosyncratic, less predictable, largely dose independent, and typically driven by hypersensitivity reactions involving the immune system.[5] Although type B reactions are less frequent (< 20%) than type A reactions, they tend to be more severe and more often lead to the withdrawal of a drug from the market.[6] One of the most common

[1]Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu 51010, Estonia; [2]Institute of Molecular and Cell Biology, University of Tartu, Tartu 51010, Estonia; [3]Wellcome Centre for Human Genetics, Nuf eld Department of Medicine, University of Oxford, Oxford OX3 7BN, UK; [4]Big Data Institute at the Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford OX3 7FZ, UK; [5]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN 37232, USA; [6]Institute of Computer Science, University of Tartu, Tartu 51009, Estonia; [7]Division of Rheumatology, In ammation and Immunity, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA; [8]Division of Genetics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA; [9]Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA; [10]Department of Biomedical Informatics, Harvard Medical School, Boston, MA 02115, USA; [11]Center for Data Sciences, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA; [12]Department of Epidemiology Research, Statens Serum Institut, Copenhagen 2300, Denmark; [13]23andMe, Inc., Sunnyvale, CA 94086, USA; [14]Centre for Genetics and Genomics Versus Arthritis, Manchester Academic Health Science Centre, University of Manchester, Manchester M13 9PT, UK; [15]STACC, Tartu 51009, Estonia; [16]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232, USA; [17]National Institute for Health Research Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford OX3 7LE, UK; [18]Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuf eld Department of Population Health, University of Oxford, Oxford OX3 7LF, UK; [19]Medical Research Council Population Health Research Unit (MRC PHRU), Nuf eld Department of Population Health, University of Oxford, Oxford OX3 7LF, UK; [20]Program in Medical and Population Genetics, Broad Institute, Cambridge, MA 02142, USA; [21]Department of Pharmacology, Vanderbilt University School of Medicine, TN 37232, USA; [22]Institute for Immunology & Infectious Diseases, Murdoch University, Murdoch, WA 6150, Australia; [23]Department of Clinical Sciences, Lund University Diabetes Centre, 214 28 Malmo ¨, Sweden; [24]Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki 00014, Finland
[25]These authors contributed equally
*Correspondence: lili.milani@ut.ee
https://doi.org/10.1016/j.ajhg.2020.08.008 .

causes of type B reactions are antibiotics, [5] typically from the beta-lactam class, with the prevalence of penicillin allergy estimated to be as high as 25% in some settings. [7,8] Despite the relative frequency of such reactions, there are very few studies of the genetic determinants of penicillin allergy. [9,10] This underscores the need for a better understanding of the mechanisms and risk factors, including the role of genetic variation, that contribute to these reactions.

The increasing availability of genetic and phenotypic data in large biobanks provides an opportune means for investigating the role of genetic variation in drug-induced hypersensitivity reactions. In the present study, we sought to identify genetic risk factors underlying penicillin-induced hypersensitivity reactions by harnessing data from the Estonian Biobank (EstBB), UK Biobank (UKBB), and Vanderbilt University Medical Center's (VUMC) DNA Biobank (BioVU), with further replication in the 23andMe research cohort.

Subjects and Methods

Study Subjects and Phenotype DeÞnitions

We studied individual-level genotypic and phenotypic data of 52,000 participants from the Estonian Biobank (EstBB), 500,000 participants from UK Biobank (UKBB), and a subset of 67,323 individuals from BioVU, the VUMC biorepository linked to de-identi ed electronic health records with self-reported European ancestry. [11] EstBB, UKBB, and BioVU are population- or hospital-based cohorts, providing a rich variety of phenotypic and health-related information collected for each participant. All participants have signed a consent form to allow follow-up linkage. In UKBB and EstBB we extracted information on penicillin allergy by searching the records of the participants for the Z88.0 ICD10 code indicating patient-reported allergy status to penicillin. Information on phenotypic features like age and gender were obtained from the biobank recruitment records. We also extracted likely penicillin allergies in EstBB from the recruitment questionnaires and free text elds of the electronic health records (EHRs) using a rule-based approach (see Supplemental Subjects and Methods for further details). In BioVU there were no records of Z88.0 diagnoses, so we used drug allergy labels from the allergy section of the EHRs, which includes adverse drug reactions reported by an individual or observed by the health care provider (Supplemental Subjects and Methods).

This study was approved by the Research Ethics Committee of the University of Tartu (Approval number 288/M-18) and conducted using the UK Biobank Resource under Application Number 11867.

Genome-wide Study and Meta-analysis

The details on genotyping, quality control, and imputation are fully described elsewhere for EstBB [12,13] and UKBB;[14] see Supplemental Subjects and Methods for further details. In EstBB, we conducted the penicillin GWAS on 44,348 individuals, including 1,320 case subjects with self-reported allergy to beta-lactam drugs or penicillin and 43,028 control subjects. In the UKBB, GWAS on penicillin allergy (de ned using ICD-10 code Z88.0) was performed among 15,782 case subjects and 370,782 control subjects. In BioVU, GWAS on penicillin allergy (de ned using drug allergy labels in the EHR) was performed among 12,294 case subjects and 38,284 control subjects. For all three cohorts, the GWAS was performed with SAIGE [15] including related individuals and adjusting for the rst ten principal components (PCs) of the genotype matrix, as well as for age or birth year, sex (see Supplemental Subjects and Methods), and in BioVU, additionally for EHR length (years). We performed meta-analysis of 19,724,685 markers (with minor allele frequency [MAF] > 0.1%) and SNP effect estimates and their standard errors were combined in a xed effects model with the inverse variance weighted method using the METAL software. [16] Results were visualized with the R software (3.3.2) (see Web Resources).

HLA-Typing

HLA imputation of the EstBB genotype data was performed at the Broad Institute using the SNP2HLA tool. [17] The imputation was done for genotype data generated on the Global Screening Array v1, and after quality control the four-digit HLA alleles of 22,554 individuals were used for analysis. In UKBB we used four-digit imputed HLA data released by UKBB (seeWeb Resources). [14] The imputation process, performed using HLA*IMP:02, [18] is described fully elsewhere[14] and in the Supplemental Subjects and Methods . For the BioVU cohort, four-digit HLA-typing was imputed from SNP data with the SNP2HLA tool (Supplemental Subjects and Methods).

We performed separate additive logistic regression analysis with the called HLA alleles using R glm function in EstBB, UKBB, and BioVU (see Supplemental Subjects and Methods for further details). Meta-analysis of 164 HLA alleles present in all three cohorts was performed with the GWAMA software tool. [19] A Bonferroni-corrected p value threshold of 3.05 3 10 4 was applied based on the number of tested alleles (0.05/164).

For detection of the strongest tagging SNP for the HLA-B*55:01 allele, we calculated Pearson correlation coef - cients between the HLA-B*55:01 allele and all the SNPs within 5 50 kb of the HLA-B region using the cor function in R (3.3.2) (see Web Resources).

HLA-B*55:01 Replication

We performed replication analysis of the HLA-B*55:01 allele in 87,996 case subjects and 1,031,087 control subjects of European ancestry (close relatives removed) from the 23andMe research cohort using an additive logistic regression model (see details in the Supplemental Subjects and Methods). The self-reported phenotype of penicillin

allergy was de ned based on questionnaire data as a positive allergy test or allergic symptoms related to penicillin exposure (see Supplemental Subjects and Methods for further details). Meta-analysis of the HLA-B*55:01 association across the four cohorts was performed with the GWAMA software tool [19] and results were visualized with R software (3.3.2) (see Web Resources).

Results

Genome-wide Association Analysis of Penicillin Allergy

To discover genetic factors that may predispose to penicillin allergy, we conducted a genome-wide association study (GWAS) of 19.7 million single-nucleotide polymorphisms (SNPs) and insertions/deletions in UKBB, EstBB, and BioVu (MAF in all cohorts > 0.1%) among individuals with European ancestry. Case subjects were de ned as participants with a Z88.0 ICD10 code ("Allergy status to penicillin"), which indicates a reported history of penicillin allergy (previously ICD9 "personal history of allergy to penicillin"). In total, we identi ed 15,782 individuals (4.1% of the total cohort size of 386,564) in UKBB with this diagnostic code. However, the corresponding number of case subjects in EstBB was only 7 (0.01% of the total cohort size of 51,936) and zero in BioVu, suggesting heterogeneity in the use of the Z88.0 ICD10 code in different countries. We therefore also identi ed participants that had reported drug allergy at recruitment in EstBB and categorized the EstBB self-reported reactions by drug class, using the Anatomical Therapeutic Chemical (ATC) Classi cation System code J01C* (beta-lactam antibacterials, penicillins) to match this to the respective Z88.0 ICD10 code. We also extracted 321 individuals with mentions of penicillin allergy in the free text elds of their EHR. This resulted in 1,320 (2.5%) case subjects with penicillin allergy in EstBB. We validated the approach in EstBB by evaluating the association between the number of lled (i.e., prescribed and purchased) penicillin (using the ATC code J01C*) prescriptions per person and self-reported penicillin allergy. Using Poisson regression analysis, we identi ed a negative association among individuals with self-reported allergy in EstBB on the number of lled penicillin prescriptions (p value 2.41 3 10 ^{15}, estimate 0.18, i.e., 16% lower penicillin prescription count for individuals with penicillin allergy). In BioVU, we used drug allergy labels from the allergy section of the EHR to identify 12,294 case subjects (18.3% of the total cohort of genotyped individuals of 67,323), which is consistent with previous penicillin allergy reports using drug allergy labels. [20] To characterize the proportion of severe reactions (anaphylaxis) to penicillin among our phenotype, we analyzed the self-reported reactions among 1,017 individuals in EstBB and found that around 3% (n ¼ 31) of the participants reported anaphylaxis and 4% (n ¼ 42) some form of breathing dif culties. In the BioVU cohort, 5% of participants (n ¼ 673 out of 12,294 with penicillin allergy label) reported anaphylaxis. These gures indicate that our phenotype likely captures less-severe forms of penicillin hypersensitivity.

We then meta-analyzed the results of the GWASes in these three cohorts and identi ed two genome-wide signi cant ($p < 5 \times 10^{-8}$) signals for penicillin allergy. The top hit on chromosome 6 was located in the major histocompatibility complex (MHC) region (rs114892859, MAF(EstBB) ¼ 0.7%, MAF(UKBB) ¼ 2%, MAF(BioVU) ¼ 2%; p value 1.29 3 10 ^{29}; OR 1.47 95% CI 1.38–1.57) (Figures 1A and S1, Table S1). We also identi ed a further signal for rs2476601, a missense variant in PTPN22 on chromosome 1 (p value 2.68 3 10 ^{9}; OR 1.09 95% CI 1.06–1.12).

Fine-Mapping the Penicillin Allergy-Associated HLA Locus

To further characterize the identi ed association with penicillin allergy, we performed a functional annotation analysis with FUMA (Functional Mapping and Annotation of Genome-Wide Association Studies). [21] We detected an independent intronic lead SNP for the penicillin allergy meta-analysis (GWAS lead variant rs114892859, p value 1.29 3 10 ^{29}) in MICA (Figure 1B). When testing the SNP for expression quantitative trait locus (eQTL) associations in blood based on data from the eQTLGen Consortium, [22] the variant appeared to be associated with the expression levels of several nearby genes, with the most signi cant being PSORS1C3 (p value 8.10 3 10 ^{62}) and MICA (p value 1.21 3 10 ^{52}) (Table S2). We further performed an in silico investigation of the lead SNP rs114892859 and its best proxy (rs144626001, the only proxy with $r^2 > 0.9$ in UKBB and EstBB) in HaploReg v.4 to explore annotations and impact of the non-coding variant. [23] rs114892859 in particular had several annotations indicative of a regulatory function, including its location in both promoter and enhancer marks in T cells and evidence of RNA polymerase II binding. [24,25] Interestingly, its proxy is more likely to be deleterious based on the scaled Combined Annotation Dependent Depletion (CADD) score (scaled score of 15.78 for rs144626001 (C/T) and 4.47 for rs114892859 (G/T)). [26,27] To assess the association of the rs114892859 variant with self-reported penicillin allergy in non-European ancestries, we used the recently developed Pan-UKB resource (see Web Resources) and retrieved summary statistics for individuals of Central/South Asian, African, East Asian, and Middle Eastern (Table S3) ancestries. We did not nd an association with penicillin allergy in these other ancestry groups. Neither did we nd any association of the rs114892859 variant with penicillin allergy (p value 0.288; OR 0.67 95% CI 0.14–1.19) in a subset of 14,416 BioVU individuals with self-reported African ancestry, including 1,894 case subjects and 9,539 control subjects. Nevertheless, these sample sizes are substantially smaller than the European-ancestry groups we studied and larger cohorts of diverse ancestries will be needed to provide more de nitive insights.

Figure 1. Manhattan Plot and HLA Locus of the Genome-wide Association Study of Penicillin Allergy
The X axes indicate chromosomal positions and Y axes $\log_{10}$ of the p Values.
(A) Each dot represents a single-nucleotide polymorphism (SNP). The dotted line indicates the genome-wide signi cance (p value < 5.0 3 10^{-8}) p value threshold.
(B) SNPs are colored according to their linkage disequilibrium (LD; based on the 1000 Genomes phase3 EUR reference panel) with the lead SNP. The SNP marked with a purple diamond is the lead SNP rs114892859.

Due to the high LD in the MHC region, we used imputed SNP to HLA typing data available at four-digit resolution [28] for up to 22,554, 488,377, and 67,323 individuals from the Estonian, UK, and BioVU cohorts, respectively, to further ne-map the identi ed HLA association with penicillin allergy. In all cohorts a shared total of 104 alleles at four-digit level were present for all of the MHC class I genes (HLA-A, HLA-B, HLA-C) and 60 alleles for three of the classical MHC class II genes (HLA-DRB1, HLA-DQA1, HLA-DQB1). To assess the variation in the frequencies of the HLA alleles in different populations, we compared the obtained allele frequencies in EstBB and UKBB (Table S4) with the

frequencies of HLA alleles in different European, Asian, and African populations reported in the HLA frequency database (Figures S2 and S3, Table S5).

We then used an additive logistic regression model to test for associations between different four-digit HLA alleles and penicillin allergy in UKBB, EstBB, and BioVU. The results from these three cohorts were meta-analyzed, using a Bonferroni-corrected p value threshold ($0.05/164 = 3.05 \times 10^{-4}$, where 164 is the number of meta-analyzed HLA alleles). One of the two results that surpassed the threshold had discordant effects in the tested cohorts (Table S6). The only association with the same directional effect in all three cohorts that we detected for penicillin allergy was the HLA-B*55:01 allele (p value 2.04×10^{-31}; OR 1.41 95% CI 1.33–1.49; Table S6), which is tagged ($r^2 > 0.95$) by the GWAS lead variant rs114892859 (Table S7). We performed a separate meta-analysis for the HLA-B*55:01 allele in all case subjects from BioVU and EstBB (p value 1.98×10^{-8}; OR 1.32 95% CI 1.20–1.45) and compared it to a meta-analysis where severe reactions of anaphylaxis were excluded. Despite the smaller sample size, the estimates from this analysis were similar (p value 1.28×10^{-8}; OR 1.33 95% CI 1.20–1.46), indicating that the association is not driven by more severe hypersensitivity reactions.

Replication of the HLA-B*55:01 Association with Penicillin Allergy

To further con rm association with penicillin allergy, we analyzed the association of the HLA-B*55:01 allele with self-reported penicillin allergy among 87,996 case subjects and 1,031,087 control subjects of European ancestry from the 23andMe research cohort. We observed an association (p value 1.00×10^{-47}; OR 1.30 95% CI 1.25–1.34; Figure 2) with a similar effect size as seen for the HLA-B*55:01 allele in the meta-analysis of the EstBB, UKBB, and BioVU. Meta-analysis of estimates for HLA-B*55:01 from the discovery and replication cohorts demonstrated a 33% higher relative odds of penicillin allergy among carriers of the allele (p value 1.15×10^{-77}; OR 1.33 95% CI 1.29–1.37; Figure 2).

Further Associations at HLA-B*55:01

Finally, we used the Open Targets Genetics platform's UKBB PheWAS data[29] to further characterize the association of the GWAS lead variant (and HLA-B*55:01 allele tag-SNP) rs114892859 with other traits. We found associations with lower lymphocyte counts (p value 9.21×10^{-14},

Table 3. HFI spectral response diagnostic parameters[a] for the band-average, and sub-band-average (see Sect. 3.1, Table 2), spectra (see also Table 4).

Spectrum	ν_{on} [GHz]		ν_{o} [GHz]		$\Delta\nu$ [GHz]		ν_{cen} [GHz]		ν_{e} [GHz]		$\int \tau d\nu$	
100-avg	84.4	0.3	117.36	0.05	32.9	0.3	100.89	0.14	101.31	0.05	0.304	0.003
100-DetSet1	84.77	0.09	117.81	0.05	33.03	0.11	101.29	0.05	101.43	0.07	0.265	0.002
100-DetSet2	84.29	0.18	117.14	0.05	32.85	0.19	100.72	0.09	101.25	0.06	0.321	0.003
143-avg	119.994	0.018	165.76	0.04	45.76	0.05	142.875	0.020	142.709	0.015	0.3669	0.0006
143-DetSet1	120.05	0.03	160.18	0.09	40.13	0.10	140.12	0.05	141.45	0.03	0.4614	0.0017
143-DetSet2	118.95	0.08	164.9	0.8	45.9	0.8	141.9	0.4	142.27	0.02	0.379	0.007
143-SWBs	120.17	0.03	166.308	0.018	46.14	0.04	143.238	0.018	143.96	0.03	0.3123	0.0007
217-avg	188.892	0.011	253.419	0.007	64.527	0.013	221.156	0.006	221.914	0.005	0.33850	0.00012
217-DetSet1	183.3	0.3	253.606	0.020	70.3	0.3	218.46	0.13	220.548	0.009	0.3053	0.0011
217-DetSet2	182.159	0.013	253.592	0.007	71.433	0.016	217.875	0.007	220.614	0.009	0.34838	0.00018
217-SWBs	189.02	0.03	253.247	0.013	64.22	0.04	221.136	0.017	222.957	0.008	0.3226	0.0002
353-avg	306.8	0.6	408.22	0.02	101.4	0.6	357.5	0.3	361.289	0.008	0.335	0.002
353-DetSet1	303.582	0.015	406.333	0.017	102.75	0.02	354.957	0.011	359.156	0.011	0.29902	0.00014
353-DetSet2	318.885	0.014	407.86	0.02	88.97	0.03	363.372	0.013	360.870	0.012	0.28730	0.00015
353-SWBs	306.3	0.4	408.81	0.03	102.5	0.4	357.56	0.18	361.921	0.011	0.3575	0.0013
545-avg	469.5	0.5	640.81	0.03	171.3	0.5	555.2	0.3	557.54	0.03	0.2612	0.0008
545-DetSet1	466.44	0.02	642.36	0.04	175.91	0.04	554.40	0.02	557.86	0.03	0.28031	0.00013
545-DetSet2	470.9	0.3	638.52	0.11	167.6	0.4	554.73	0.17	556.85	0.05	0.2143	0.0005
857-avg	743.9	0.4	989.78	0.08	245.9	0.4	866.8	0.2	862.68	0.05	0.2165	0.0004
857-DetSet1	736.9	0.7	990.38	0.06	253.4	0.7	863.7	0.4	863.42	0.06	0.2121	0.0006
857-DetSet2	741.79	0.13	987.01	0.10	245.22	0.17	864.40	0.08	861.74	0.07	0.21419	0.00017

Notes.[(a)] The parameters shown here are introduced in Sect. 2.3.

such that the sum total within the desired detector grouping is unity as follows

$$w_{NETi} = \frac{1/(NET_i)^2}{W} \quad \text{where} W = \sum_i (1/(NET_i)^2): \qquad (5)$$

The detector NETs and the w_{NETi} factors can be found in Planck Collaboration (2013). Two detectors have been omitted from contributing towards the band-average spectra due to random telegraphic signal (RTS), i.e., popcorn noise: 143 GHz-8 and 545 GHz-3. The w_i factor introduced above is a general concept with the w_{NETi} factor in this section representing a special case of the concept. Other special cases of the w_i factor will be introduced later.

3.1.2. Detector channel-map contribution weighting

The NET can be scan-normalized using the individual-detector pixel-hit maps available as standard data products (these will be made publicly available in the final release of Planck data if not earlier, further details on the hit-maps can be found in Planck Collaboration 2013), i.e.,

$$w_{m,i} = \frac{\left(\sum_{;} H_{m,i}(;)\right)/(NET_i)^2}{W}; \qquad (6)$$

where W is a normalization term as described above (see Eq. (5)), $H_{m,i}(;)$ represents the hit-map counts for a given detector, sky position, and a given map, m, (e.g., full-survey, nominal-survey, survey 1, etc.); the $\sum_{;}$ term represents summing over the entire map. A similar approach could be taken where the $\sum_{;}$ summation is omitted; instead of a single $w_{m,i}$ factor for a given map, m, this would result in a map of weighting factors of the same spatial resolution as the map, $w_{m,i}(;,)$. An example of this, using the nominal survey and survey 1 results

Table 4. HFI spectral response effective frequencies[a] for the band-average, and sub-band-average, spectra (see also Table 3).

Spectrum	$\nu_{=1}$ [GHz]		$\nu_{=2}$ [GHz]		$\nu_{=4}$ [GHz]	
100-avg	100.36	0.05	103.24	0.05	105.25	0.04
100-DetSet1 . .	100.49	0.07	103.35	0.06	105.34	0.06
100-DetSet2 . .	100.31	0.07	103.19	0.06	105.21	0.05
143-avg	141.362	0.015	145.457	0.014	148.234	0.013
143-DetSet1 . .	140.11	0.03	144.22	0.02	147.05	0.02
143-DetSet2 . .	140.91	0.02	145.05	0.02	147.90	0.02
143-SWBs	142.64	0.03	146.63	0.02	149.28	0.02
217-avg	220.111	0.005	225.517	0.006	229.096	0.007
217-DetSet1 . .	218.666	0.009	224.312	0.009	228.038	0.010
217-DetSet2 . .	218.697	0.009	224.429	0.009	228.200	0.010
217-SWBs	221.241	0.008	226.395	0.008	229.834	0.010
353-avg	358.563	0.008	366.763	0.009	372.192	0.010
353-DetSet1 . .	356.386	0.011	364.744	0.012	370.302	0.013
353-DetSet2 . .	358.409	0.012	365.850	0.012	370.837	0.013
353-SWBs	359.158	0.011	367.455	0.012	372.930	0.014
545-avg	552.22	0.05	567.596	0.017	576.778	0.014
545-DetSet1 . .	552.43	0.06	568.12	0.02	577.458	0.017
545-DetSet2 . .	551.76	0.08	566.48	0.03	575.32	0.02
857-avg	854.69	0.11	877.724	0.018	891.462	0.016
857-DetSet1 . .	855.33	0.16	878.67	0.02	892.59	0.02
857-DetSet2 . .	853.89	0.17	876.53	0.03	890.03	0.02

Notes.[(a)] The effective frequencies shown here are calculated using Eq. (4).

11. Roden, D.M., Pulley, J.M., Basford, M.A., Bernard, G.R., Clayton, E.W., Balser, J.R., and Masys, D.R. (2008). Development of a large-scale de-identi ed DNA biobank to enable personalized medicine. Clin. Pharmacol. Ther. 84, 362–369.
12. Mitt, M., Kals, M., Pa¨rn, K., Gabriel, S.B., Lander, E.S., Palotie, A., Ripatti, S., Morris, A.P., Metspalu, A., Esko, T., et al. (2017). Improved imputation accuracy of rare and low-frequency variants using population-speci c high-coverage WGS-based imputation reference panel. Eur. J. Hum. Genet. 25, 869–876.
13. Kals, M., Nikopensius, T., La¨ll, K., Pärn, K., Sikka, T.T., Suvisaari, J., Salomaa, V., Ripatti, S., Palotie, A., Metspalu, A., et al. (2019). Advantages of genotype imputation with ethnically matched reference panel for rare variant association analyses. bioRxiv. https://doi.org/10.1101/579201 .
14. Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L.T., Sharp, K., Motyer, A., Vukcevic, D., Delaneau, O., O'Connell, J., et al. (2018). The UK Biobank resource with deep phenotyping and genomic data. Nature 562, 203–209.
15. Zhou, W., Nielsen, J.B., Fritsche, L.G., Dey, R., Gabrielsen, M.E., Wolford, B.N., LeFaive, J., VandeHaar, P., Gagliano, S.A., Gifford, A., et al. (2018). Ef ciently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. Nat. Genet. 50, 1335–1341.
16. Willer, C.J., Li, Y., and Abecasis, G.R. (2010). METAL: fast and ef cient meta-analysis of genomewide association scans. Bioinformatics 26, 2190–2191.
17. Jia, X., Han, B., Onengut-Gumuscu, S., Chen, W.-M., Concannon, P.J., Rich, S.S., Raychaudhuri, S., and de Bakker, P.I.W. (2013). Imputing amino acid polymorphisms in human leukocyte antigens. PLoS ONE 8, e64683.
18. Dilthey, A., Leslie, S., Moutsianas, L., Shen, J., Cox, C., Nelson, M.R., and McVean, G. (2013). Multi-population classical HLA type imputation. PLoS Comput. Biol. 9, e1002877.
19. Mägi, R., and Morris, A.P. (2010). GWAMA: software for genome-wide association meta-analysis. BMC Bioinformatics 11, 288.
20. Zhou, L., Dhopeshwarkar, N., Blumenthal, K.G., Goss, F., Topaz, M., Slight, S.P., and Bates, D.W. (2016). Drug allergies documented in electronic health records of a large healthcare system. Allergy 71, 1305–1313.
21. Watanabe, K., Taskesen, E., van Bochoven, A., and Posthuma, D. (2017). Functional mapping and annotation of genetic associations with FUMA. Nat. Commun. 8, 1826.
22. Võsa, U., Claringbould, A., Westra, H.-J., Bonder, M.J., Deelen, P., Zeng, B., Kirsten, H., Saha, A., Kreuzhuber, R., Kasela, S., et al. (2018). Unraveling the polygenic architecture of complex traits using blood eQTL metaanalysis. bioRxiv. https://doi.org/10.1101/447367 .
23. Ward, L.D., and Kellis, M. (2012). HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. Nucleic Acids Res. 40, D930–D934 .
24. Kundaje, A., Meuleman, W., Ernst, J., Bilenky, M., Yen, A., Heravi-Moussavi, A., Kheradpour, P., Zhang, Z., Wang, J., Ziller, M.J., et al.; Roadmap Epigenomics Consortium (2015). Integrative analysis of 111 reference human epigenomes. Nature 518, 317–330.
25. Myers, R.M., Stamatoyannopoulos, J., Snyder, M., Dunham, I., Hardison, R.C., Bernstein, B.E., Gingeras, T.R., Kent, W.J., Birney, E., Wold, B., et al.; ENCODE Project Consortium (2011). A user's guide to the encyclopedia of DNA elements (ENCODE). PLoS Biol. 9, e1001046.
26. Rentzsch, P., Witten, D., Cooper, G.M., Shendure, J., and Kircher, M. (2019). CADD: predicting the deleteriousness of variants throughout the human genome. Nucleic Acids Res. 47 (D1), D886–D894

41. Romano, A., Blanca, M., Torres, M.J., Bircher, A., Aberer, W., Brockow, K., Pichler, W.J., Demoly, P.; ENDA; and EAACI (2004). Diagnosis of nonimmediate reactions to beta-lactam antibiotics. Allergy *59*, 1153–1160.
42. Adam, J., Pichler, W.J., and Yerly, D. (2011). Delayed drug hypersensitivity: models of T-cell stimulation. Br. J. Clin. Pharmacol. *71*, 701–707.
43. Hertl, M., Geisel, J., Boecker, C., and Merk, H.F. (1993). Selective generation of CD8+ T-cell clones from the peripheral blood of patients with cutaneous reactions to beta-lactam antibiotics. Br. J. Dermatol. *128*, 619–626.
44. Pavlos, R., McKinnon, E.J., Ostrov, D.A., Peters, B., Buus, S., Koelle, D., Chopra, A., Schutte, R., Rive, C., Redwood, A., et al. (2017). Shared peptide binding of HLA Class I and II alleles associate with cutaneous nevirapine hypersensitivity and identify novel risk alleles. Sci. Rep. *7*, 8653.
45. Pirmohamed, M., Ostrov, D.A., and Park, B.K. (2015). New genetic findings lead the way to a better understanding of fundamental mechanisms of drug hypersensitivity. J. Allergy Clin. Immunol. *136*, 236–244.
46. Meng, X., Jenkins, R.E., Berry, N.G., Maggs, J.L., Farrell, J., Lane, C.S., Stachulski, A.V., French, N.S., Naisbitt, D.J., Pirmohamed, M., and Park, B.K. (2011). Direct evidence for the formation of diastereoisomeric benzylpenicilloyl haptens from benzylpenicillin and benzylpenicillenic acid in patients. J. Pharmacol. Exp. Ther. *338*, 841–849.
47. Weltzien, H.U., and Padovan, E. (1998). Molecular features of penicillin allergy. J. Invest. Dermatol. *110*, 203–206.
48. Chessman, D., Kostenko, L., Lethborg, T., Purcell, A.W., Williamson, N.A., Chen, Z., Kjer-Nielsen, L., Mifsud, N.A., Tait, B.D., Holdsworth, R., et al. (2008). Human leukocyte antigen class I-restricted activation of CD8+ T cells provides the immunogenetic basis of a systemic drug hypersensitivity. Immunity *28*, 822–832.
49. Ostrov, D.A., Grant, B.J., Pompeu, Y.A., Sidney, J., Harndahl, M., Southwood, S., Oseroff, C., Lu, S., Jakoncic, J., de Oliveira, C.A.F., et al. (2012). Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. Proc. Natl. Acad. Sci. USA *109*, 9959–9964.
50. Illing, P.T., Vivian, J.P., Dudek, N.L., Kostenko, L., Chen, Z., Bharadwaj, M., Miles, J.J., Kjer-Nielsen, L., Gras, S., Williamson, N.A., et al. (2012). Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. Nature *486*, 554–558.
51. Aguiar, V.R.C., César, J., Delaneau, O., Dermitzakis, E.T., and Meyer, D. (2019). Expression estimation and eQTL mapping for HLA genes with a personalized pipeline. PLoS Genet. *15*, e1008091.
52. Génin, E., Schumacher, M., Roujeau, J.C., Naldi, L., Liss, Y., Kazma, R., Sekula, P., Hovnanian, A., and Mockenhaupt, M. (2011). Genome-wide association study of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Europe. Orphanet J. Rare Dis. *6*, 52.
53. Bateman, A.; and UniProt Consortium (2019). UniProt: a worldwide hub of protein knowledge. Nucleic Acids Res. *47* (D1), D506–D515.
54. Duan, Q., Li, H., Gao, C., Zhao, H., Wu, S., Wu, H., Wang, C., Shen, Q., and Yin, T. (2019). High glucose promotes pancreatic cancer cells to escape from immune surveillance via AMPK-Bmi1-GATA2-MICA/B pathway. J. Exp. Clin. Cancer Res. *38*, 192.
55. Shafi, S., Vantourout, P., Wallace, G., Antoun, A., Vaughan, R., Stanford, M., and Hayday, A. (2011). An NKG2D-mediated human lymphoid stress surveillance response with high interindividual variation. Sci. Transl. Med. *3*, 113ra124.
56. Stanford, S.M., Rapini, N., and Bottini, N. (2012). Regulation of TCR signalling by tyrosine phosphatases: from immune homeostasis to autoimmunity. Immunology *137*, 1–19.
57. Stanford, S.M., and Bottini, N. (2014). PTPN22: the archetypal non-HLA autoimmunity gene. Nat. Rev. Rheumatol. *10*, 602–611.
58. Begovich, A.B., Carlton, V.E.H., Honigberg, L.A., Schrodi, S.J., Chokkalingam, A.P., Alexander, H.C., Ardlie, K.G., Huang, Q., Smith, A.M., Spoerke, J.M., et al. (2004). A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. Am. J. Hum. Genet. *75*, 330–337.
59. Cirulli, E.T., Nicoletti, P., Abramson, K., Andrade, R.J., Bjornsson, E.S., Chalasani, N., Fontana, R.J., Hallberg, P., Li, Y.J., Lucena, M.I., et al.; Drug-Induced Liver Injury Network (DILIN) investigators; and International DILI consortium (iDILIC) (2019). A Missense Variant in PTPN22 is a Risk Factor for Drug-induced Liver Injury. Gastroenterology *156*, 1707–1716.e2.
60. Chen, H., Hayashi, G., Lai, O.Y., Dilthey, A., Kuebler, P.J., Wong, T.V., Martin, M.P., Fernandez Vina, M.A., McVean, G., Wabl, M., et al. (2012). Psoriasis patients are enriched for genetic variants that protect against HIV-1 disease. PLoS Genet. *8*, e1002514.
61. Winchester, R., Giles, J., Jadon, D., Haroon, M., McHugh, N., and FitzGerald, O. (2016). Implications of the diversity of class I HLA associations in psoriatic arthritis. Clin. Immunol. *172*, 29–33.
62. Shenoy, E.S., Macy, E., Rowe, T., and Blumenthal, K.G. (2019). Evaluation and Management of Penicillin Allergy: A Review. JAMA *321*, 188–199.
63. Jani, Y.H., Williams, I., and Krishna, M.T. (2020). Sustaining and spreading penicillin allergy delabelling: A narrative review of the challenges for service delivery and patient safety. Br. J. Clin. Pharmacol. *86*, 548–559.
64. Sousa-Pinto, B., Fonseca, J.A., and Gomes, E.R. (2017). Frequency of self-reported drug allergy: A systematic review and meta-analysis with meta-regression. Ann. Allergy Asthma Immunol. *119*, 362–373.e2.
65. Mallal, S., Nolan, D., Witt, C., Masel, G., Martin, A.M., Moore, C., Sayer, D., Castley, A., Mamotte, C., Maxwell, D., et al. (2002). Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet *359*, 727–732.
66. Chen, P., Lin, J.-J., Lu, C.-S., Ong, C.-T., Hsieh, P.F., Yang, C.-C., Tai, C.-T., Wu, S.-L., Lu, C.-H., Hsu, Y.-C., et al.; Taiwan SJS Consortium (2011). Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N. Engl. J. Med. *364*, 1126–1133.
67. McCormack, M., Alfirevic, A., Bourgeois, S., Farrell, J.J., Kasperavičiūtė, D., Carrington, M., Sills, G.J., Marson, T., Jia, X., de Bakker, P.I.W., et al. (2011). HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N. Engl. J. Med. *364*, 1134–1143.